Editorial

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Liver sinusoidal cells collecting MHC-I molecules: You can't get enough of a good thing

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See Article, pages 600–608

The liver is constantly confronted with a variable influx of microbial and nutritional components from the gut. The incoming cargo is mostly harmless, but also has the potential to cause liver damage or infection. Various types of liver-resident antigen-presenting cells guard the hepatic sinusoids and maintain immune tolerance under homoestatic conditions [1]. However, in the presence of damage or danger, these cells can potently activate the effector responses of T cells and induce inflammation [2]. The role of liver dendritic cells (DCs), Kupffer cells (KCs) and liver sinusoidal endothelial cells (LSECs) in hepatic immune regulation is well established; however, the contribution of hepatic stellate cells (HSCs) to immune responses in the liver is controversially discussed [3–5].

In their study in this issue of the *Journal of Hepatology*, Schölzel *et al.* investigated the role of HSCs in activating CD8 T cells. CD8 T cells recognize antigen peptides bound to MHC I molecules; these peptides usually are derived by proteasomal degradation and represent endogenous antigens [6]. However, some cell types, including DCs, LSECs and KCs, have the ability to load onto their MHC I molecules peptides that were derived from exogenous antigens [7]. This so called 'cross-presentation' is a means to induce CD8 T cell responses, e.g., to blood-borne antigens [8]. Schölzel *et al.* analysed whether HSCs are able to cross-present blood-borne antigens to facilitate CD8 T cell activation. By using transgenic mice that express distinct MHC I molecules of the H-2K^b haplotype in HSCs under the control of the GFAP promoter (GFAP-K^b), and using an advanced HSC isolation strategy yielding highly pure HSCs, they found that HSCs completely lack cross-presentation competence. However, surprisingly, these GFAP-K^b mice were nonetheless able to induce specific K^b-restricted CD8 T cell activation to blood-borne antigens.

Schölzel *et al.* explain this observation by intercellular transfer of MHC I molecules from the cell-surface of HSCs to LSECs. This intercellular MHC I molecule transfer seems to be akin to 'trogocytosis' (derived from the greek word "trogo", meaning to nibble or to gnaw), a process through which membrane chunks and, with those, MHC molecules can be exchanged between immune cells at the immunological synapse [9]. The physiological relevance of trogocytosis is not entirely clear, but it seems to serve the modulation of immune responses, and can have both, reinforcing or inhibitory effects [9–11].

What then is the biological meaning of trogocytosis in the liver? Why do LSECs nibble off MHC molecules from their neighbour cells? Recently, it has been shown that in hepatotropic virus infection LSEC-mediated cross-presentation of viral antigens is important for the induction of an efficient CTL response [12]. Schölzel *et al.* assumed that the transfer of MHC-I molecules from HSCs to LSECs might improve anti-viral immunity, by facilitating cross-presentation of viral antigens even under conditions of virus-induced MHC down-regulation. Indeed, the authors showed that GFAP-K^b mice infected with adenovirus manifested K^b-restricted CTL-mediated hepatitis, although K^b in the liver was expressed only by HSCs. This finding could only be explained by transfer of K^b molecules from HSCs to cross-presenting liver cells, such as LSECs, which then induced CTL activation (Fig. 1). Note that the authors show that exchange of MHC-I molecules can occur also between HSCs and liver DCs or Kupffer cells. As DCs and KCs are cross-presenting cells like LSECs [7], it is possible that KCs or DCs might also have acquired H-2K^b molecules from HSCs and contributed to antiviral CTL activation in GFAP-K^b mice.

Although this is a sound explanation for the occurrence of trogocytosis in liver infection, the biological relevance of trogocytosis in healthy liver is not immediately obvious. Schölzel *et al.* find hepatic trogocytosis also in non-infected livers, which are replete with MHC molecules, and there is no virus-induced MHC down-regulation to be compensated. It is yet unclear how hepatic trogocytosis is regulated and whether it is increased in liver infection. Given that hepatic trogocytosis seems to occur permanently, what could its relevance be in the healthy liver? It can be assumed that hepatic trogocytosis is an energy consuming activity that is only being performed because it suits a biological need. One might speculate that hepatic trogocytosis not only safeguards antigen presentation for the induction of liver inflammation, but also for tolerance. As trogocytosis in immune cells can include the exchange of co-stimulatory molecules such as CD80 or CD86 [9,11] or co-inhibitory molecules such as PD-L1 [13], it is likely that these molecules might also be exchanged in hepatic trogocytosis and mediate activating or inhibitory

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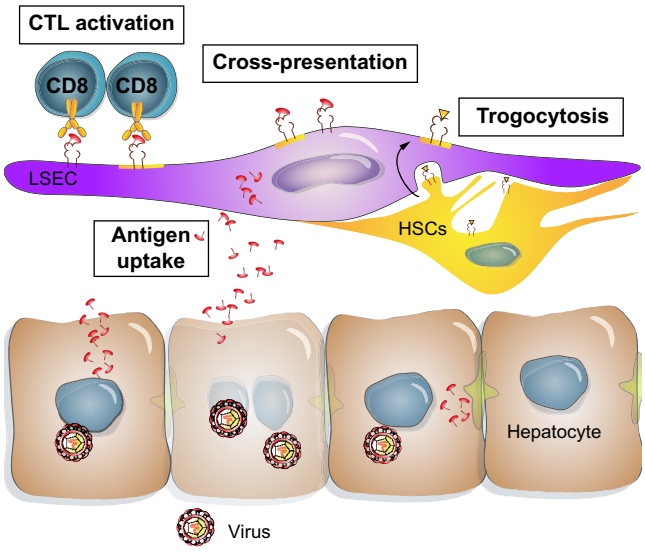

Fig. 1. Transfer of MHC-I molecules between liver cells by trogocytosis. Hepatic stellate cells (HSC) transfer MHC-I molecules to liver sinusoidal endothelial cells (LSEC) by trogocytosis. LSECs can cross-present exogenous antigen, e.g. derived from virus infected hepatocytes, and use transferred MHC-I molecules for peptide-specific activation of cytotoxic T lymphocytes (CTL).

effects to facilitate T cell activation in liver infection or T cell tolerance in healthy liver.

Moreover, it is possible that the exchange of peptide-loaded MHC molecules between various liver cell types could increase the visibility of antigen peptides for circulating T cells. This might be of particular relevance for HSCs, which locate in the perisinusoidal space and thus are somewhat hidden from circulating T cells. The display of HSC-derived MHC molecules by LSECs might enhance T cell responses to HSC-derived peptides loaded onto these MHC molecules. However, there is currently no evidence for that assumption and further investigation is needed to clarify the physiological relevance of hepatic trogocytosis. As trogocytosis is a fast process that seems to occur predominantly in the immunological synapse [9], it is also conceivable that such MHC I transfer might occur during the interaction between liver-resident cells and circulating T cells. Such transfer of MHC-I molecules from liver cells to circulating immune cells might not only shape the local immune response, but could even facilitate the transport to remote lymphatic tissues.

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Conflict of interest

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